The Contribution of a Metabolite, Trichloroacetic Acid, to the Toxicity of Tetrachloroethylene

Karen Hogan[1], Cheryl Siegel Scott[2]
Office of Research and Development, National Center for Environmental Assessment, [1]IRIS Program, [2]Washington Division

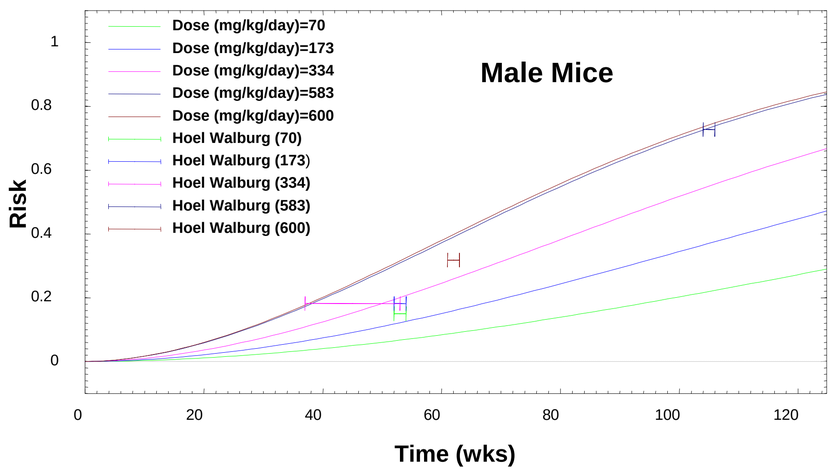
Background

Trichloroacetic acid (TCA), a metabolite of tetrachloroethylene (perchloroethylene, PERC), is associated with hepatocarcinogenicity in male and female mice (Bull et al., 1990, 2002; Daniel et al, 1993; Herren-Freund et al., 1995; Ferreira-Gonzalez, 1987; Pereira, 1996), as is PERC (NCI, 1977; NTP, 1986; JISA, 1992). There has been some suggestion that TCA does not account for all of the toxicity observed with PERC (Buben and O'Flaherty, 1985; Clewell et al., 2005). The purpose of this investigation was to compare the incidence of hepatocarcinogenicity observed with PERC exposure, with that observed with TCA exposure, in order to examine whether the TCA that is expected to be generated by PERC can account for PERC's hepatocarcinogenicity. This was carried out by pooling the separate TCA studies, fitting time-to-tumor models to the male and female mouse TCA data, and comparing the incidence of hepatocellular carcinomas expected based on the TCA studies with that observed in the two inhalation PERC bioassays in mice (NTP, 1986; JISA, 1993).

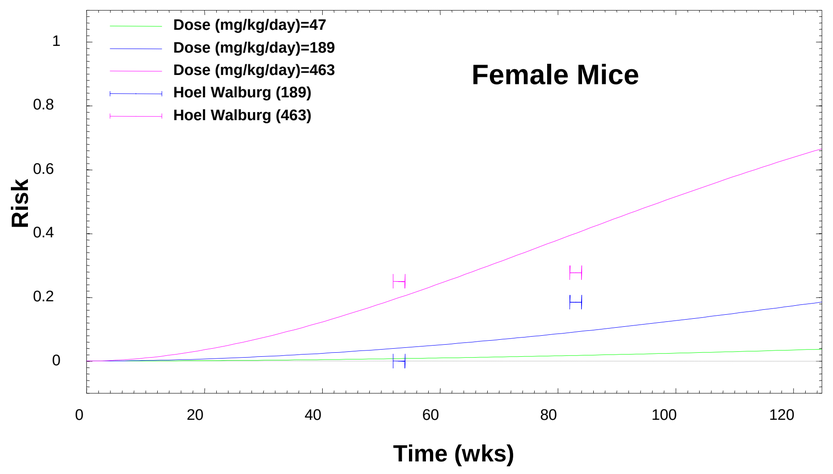
(The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the US Environmental Protection Agency.)

Data and Methods

The TCA data were collected at several intervals, all shorter than the length of the PERC bioassays. Time-to-tumor models such as the multistage-Weibull model make the greatest use of these data: $P(d) = 1- \exp [-q_0 - q_1 d - q_2 d^2 - \ldots) \bullet t^z]$,
where d = measured dose, t = time hepatocellular carcinoma was observed (at death), and q_i and z are parameters estimated for best fit of the model.



$P(d) = 1 - \exp [(-1.76 \times 10^{-5} - 3.61 \times 10^{-7} d) \times t^{1.89}]$



$P(d) = 1 - \exp [(-3.39 \times 10^{-6} - 6.10 \times 10^{-10} d^2) \times t^{1.87}]$

The level of TCA associated with each exposure level of PERC in two bioassays (NTP, 1985; JISA, 1993) was estimated using a two-step process. First the pharmacokinetic model of Reitz et al. (1996) provided the amount of total daily metabolism, then it was assumed that 60% of the total metabolites was TCA (Gearhart et al., 1993). Then the models above were applied to the TCA levels expected to have been generated in the PERC bioassays, at intervals corresponding to the times of sacrifice in the TCA studies which revealed carcinomas (week 60 for males, week 82 for females) and extrapolating to Week 104 for the final sacrifice in the PERC bioassays.

Results

The PERC studies tended to show higher hepatocellular carcinoma incidence at 104 weeks at exposure levels (>~20 mg/kg-day TCA) than predicted by the TCA studies. The power of the PERC studies was too low at the lower exposures, so these latter comparisons are more inconclusive. If TCA were the sole cause of the PERC carcinomas, the TCA data should have tended to overestimate the tumor incidence in the PERC studies at the timepoints before Week 104, due to the PERC tumor incidences before Week 104 including only unscheduled deaths and the TCA data accounting for all tumors present through scheduled termination.

Male Mice

Perc Bioassay	Weeks of Exposure	N	Perc exposure, ppm	Perc-induced TCA, mg/kg-day	Cumulative proportion with carcinomas		Obs/Pred
					Observed	Predicted	
NTP (1986)	60	49	0	0	0.0	0.0	-
		47	100	17	0.0	0.012	-
		50	200	26	0.02	0.018	1
	104	49	0	0	0.0	0.0	-
		47	100	17	0.389	0.031	13
		50	200	26	0.377	0.047	8
JISA (1993)	60	46	0	0	0.0	0.0	-
		49	10	2	0.0	0.001	-
		48	50	9	0.0	0.006	-
		49	250	23	0.0	0.016	-
	104	46	0	0	0.0	0.0	-
		49	10	2	0.011	0.004	3
		48	50	9	0.098	0.016	6
		49	250	23	0.358	0.041	9

Female Mice

Perc Bioassay	Weeks of Exposure	N	Perc exposure, ppm	Perc-induced TCA, mg/kg-day	Cumulative Proportion with Carcinomas		Obs/Pred
					Observed	Predicted	
NTP (1986)	82	45	0	0	0.0	0.0	-
		42	100	20	0.024	0.0009	27
		48	200	28	0.063	0.0018	34
	104	45	0	0	0.0	0.0	-
		42	100	20	0.287	0.0014	210
		48	200	28	0.728	0.0029	260
JISA (1993)	82	50	0	0	0.0	0.0	-
		47	10	3	0.0	0.00002	-
		48	50	11	0.0	0.0003	-
		49	250	30	0.0	0.0020	-
	104	50	0	0	0.0	0.0	-
		47	10	3	0.00002	0.00002	-
		48	50	11	0.0003	0.0003	-
		49	250	30	0.0020	0.0020	90

Discussion

- The hepatocellular carcinomas were not evaluated under a common protocol, and adenomas were not always reported by the different laboratories. Consistency among the available TCA and PERC data sets could increase if all hepatocellular tumor results were available and could be evaluated by the same set of pathologists.
- There were two notable extrapolations: 1) from relatively high TCA levels to TCA levels likely to have been generated in the available PERC bioassays but not included in the TCA studies; and 2) from Week 60 (male mice) and Week 82 (female mice) to Week 104.
- Uncertainty analysis to consider the contribution of sampling variability to the predictions is an important next step.

References

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